

## General

### Guideline Title

Systemic therapy in the curative treatment of head and neck squamous cell cancer.

### Bibliographic Source(s)

Winquist E, Agbassi C, Meyers B, Yoo J, Chan K, Head and Neck Cancer Disease Site Group. Systemic therapy in the curative treatment of head and neck squamous cell cancer. Toronto (ON): Cancer Care Ontario (CCO); 2016 Aug 10. 51 p. (Program in Evidence-based Care Guideline; no. 5-11). [91 references]

### Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

## Recommendations

### Major Recommendations

#### Recommendation 1

Concurrent chemoradiotherapy (CRT) is recommended to maximize the chance of cure in patients <71 years of age when radiotherapy (RT) is used as the definitive management for locally advanced nonmetastatic squamous cell carcinoma of the head and neck (LASCCHN).

#### Recommendation 2

For patients with resected LASCCHN considered to be at high risk of locoregional recurrence, concurrent chemoradiotherapy is recommended over RT alone to maximize the chance of cure in patients <71 years of age.

#### Recommendation 3

For patients with LASCCHN who are candidates for organ preservation strategies and would otherwise require total laryngectomy, two strategies are superior to RT alone for larynx preservation: CRT, or induction chemotherapy followed by radiation or surgery based on tumour response.

#### Recommendation 4

The addition of cetuximab to intensified RT (concomitant boost or hyperfractionated schedule) may provide an alternative option to CRT.

#### Recommendation 5

The routine use of induction chemotherapy as neoadjuvant treatment to improve overall survival is not recommended for patients with LASCCHN.

## Clinical Algorithm(s)

None provided

## Scope

### Disease/Condition(s)

Locally advanced nonmetastatic squamous cell carcinoma of the head and neck (LASCCHN)

### Guideline Category

Management

Treatment

### Clinical Specialty

Oncology

Otolaryngology

Radiation Oncology

Surgery

### Intended Users

Advanced Practice Nurses

Allied Health Personnel

Health Care Providers

Nurses

Physician Assistants

Physicians

### Guideline Objective(s)

To make recommendations, based on data from randomized controlled trials (RCTs), regarding treatment strategies for cure and/or organ preservation in patients with locally advanced nonmetastatic (Stage III to IVB) squamous cell carcinoma of the head and neck (LASCCHN)

### Target Population

Patients with locally advanced nonmetastatic squamous cell carcinoma of the head and neck (LASCCHN) being considered for curative intent treatment

### Interventions and Practices Considered

1. Concurrent chemoradiotherapy (CRT)
2. Induction chemotherapy followed by radiation or surgery
3. Addition of cetuximab to intensified radiation therapy (RT)
4. Routine use of induction chemotherapy as neoadjuvant treatment to improve overall survival (not recommended)

## Major Outcomes Considered

- Overall response rate (ORR)
- Overall survival rate (OS)
- Progression-free survival/disease-free survival (PFS/DFS)
- Recurrence-free survival (RFS)
- Locoregional control (LRC)
- Complete response (CR)
- Tumor response rate
- Larynx preservation rate
- Risk of disease progression
- Time to treatment failure (TTF)
- Quality of life (QoL)
- Adverse effects/toxicity

## Methodology

### Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

### Description of Methods Used to Collect/Select the Evidence

#### Search for Existing Guidelines

A search for existing guidelines is generally undertaken prior to searching for existing systematic reviews or primary literature. This is done with the goal of identifying existing guidelines for adaptation or endorsement in order to avoid the duplication of guideline development efforts across jurisdictions. For this project, the following sources were searched for existing guidelines that addressed the research questions:

- Practice guideline databases: Standards and Guidelines Evidence Directory of Cancer Guidelines ([SAGE](#) ) , Agency for Healthcare Research and Quality ([AHRQ](#) ) National Guideline Clearinghouse, and the [Canadian Medical Association Infobase](#) .
- The Web sites of guideline developers such as the National Institute for Health and Clinical Excellence ([NICE](#) ) , Scottish Intercollegiate Guidelines Network ([SIGN](#) ) , National Comprehensive Cancer Network ([NCCN](#) ) , American Society of Clinical Oncology ([ASCO](#) ) , New Zealand Guidelines Group ([NZGG](#) ) , and National Health and Medical Research Council- Australia ([NHMRC](#) ) were also searched.

Guidelines that were considered relevant to the objectives and the research questions were then evaluated for quality using the Appraisal of Guidelines Research and Evaluation (AGREE) II instrument. The search for existing guidelines for adaptation or endorsement did not yield an appropriate source document; therefore a search of the primary literature was required.

#### Methods

This evidence review was conducted in two planned stages: a search for systematic reviews followed by a search for primary literature. These stages are described in subsequent sections. Three individual patient data meta-analyses (MACH-NC) were considered a complete reference for all relevant studies published prior to 2000 and served as the evidence base for this document, for randomized controlled trials (RCTs) reported during that time frame.

### Search for Existing Systematic Reviews

A search for existing systematic reviews on the role of systemic chemotherapy in the management of locally advanced squamous cell carcinoma of the head and neck (LASCCHN) was conducted. Systematic reviews published as a component of practice guidelines that were not considered suitable for adaptation or endorsement were also considered eligible for inclusion in the evidence base. The Ovid interface was used to search MEDLINE and EMBASE for existing systematic reviews in this topic area. As the MACH-NC meta-analyses provided a comprehensive review of RCTs conducted from 1965 to 2000 and that compared the addition of chemotherapy to local therapy with local therapy alone, the search was limited to systematic reviews published since January 2000 and up to September 2014. The Cochrane Database of Systematic Reviews was also searched using a combination of the following search terms: induction, adjuvant, concurrent or concomitant chemotherapy, and squamous cell carcinoma of the head and neck.

Identified systematic reviews were further evaluated based on their clinical content and their relevance. Relevant systematic reviews were assessed using the 11-item Assessment of Multiple Systematic Reviews (AMSTAR) tool to determine whether they met a minimum threshold for methodological quality to be considered for inclusion in the evidence base.

### Search for Primary Literature

In addition to the selection of suitable systematic reviews, the same combination of search terms was used to conduct a broad search for primary literature in MEDLINE and EMBASE (January 2000 through February 2015). The year 2000 was used as a cut-off to minimize duplication of the MACH-NC meta-analyses. Details of the literature search strategy can be found in Appendix II of the original guideline document. Question-specific searches were also conducted for each research question in order to capture studies that may not have been retrieved by the broad search. The Cochrane Library was also searched. The proceedings of the meetings of the ASCO, American Society for Radiation Oncology (ASTRO), European Society for Medical Oncology (ESMO), and European Society for Therapeutic Radiation and Oncology (ESTRO) were searched for relevant abstracts. The reference lists of studies deemed eligible for inclusion were also hand searched for additional citations.

### Study Selection Criteria and Process

A review of the titles and abstracts that resulted from the electronic searches was carried out by one reviewer. For those items that appeared to meet the inclusion criteria, the reviewer obtained and reviewed the full text of each item. Studies were included if they were systematic reviews, meta-analyses, or randomized controlled trials (RCTs) evaluating the role of induction or concurrent chemotherapy in the management of non-metastatic squamous cell carcinoma of the head and neck (SCCHN), specifically in the hypopharynx, larynx, trachea, oral cavity, and oropharynx regions, or RCTs comparing one drug regimen including targeted agents and radiosensitizers with another drug regimen alone or in combination with locoregional treatment (radiotherapy and/or surgery). The studies had to report at least one of the following outcomes: overall survival rate (OS), disease free survival rate (DFS), tumour response rate, larynx preservation, Grade 3/4 toxicity or quality of life.

### Exclusion Criteria

- Studies that included nasopharyngeal carcinoma.
- Case reports, news reports, notes, commentaries, opinions, letters, editorials, qualitative studies
- Studies on cost-effectiveness, utility, and economics
- Studies with fewer than 30 participants
- Studies published in a language other than English, due to the lack of funding and resources for translation

Refer to the "Results" section of the original guideline document for information on studies retrieved through the literature searches.

## Number of Source Documents

- Existing Guidelines: The search for existing guidelines for adaptation or endorsement did not yield an appropriate source document.
- Existing Systematic Reviews: After full text review, five meta-analyses were included.
- Primary Literature: A total of 59 reports (49 full text articles, and 10 abstracts) met the inclusion criteria and were included as the basis for the evidence used in making the recommendations.

## Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

## Rating Scheme for the Strength of the Evidence

Not applicable

## Methods Used to Analyze the Evidence

Meta-Analysis

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

## Description of the Methods Used to Analyze the Evidence

### Data Extraction and Assessment of Study Quality and Potential for Bias

Data from the included studies were extracted by the project research methodologist. The characteristics of the study population, including the sample size and years of accrual, duration of follow-up, and the treatment options, were extracted. When reported, response, progression, and survival information were also extracted from the results of the included studies. In cases of duplicate publication for the same study, only the most recent version of the data was extracted in the results. All extracted data and information was audited by an independent auditor. Study quality was assessed based on the risk of bias and other important quality features such as the follow-up duration and rate, power calculation, and sample size. The Cochrane Risk of Bias Assessment Tool was used for the risk-of-bias assessment (see Appendix III in the original guideline document).

### Synthesizing the Evidence

When multiple randomized controlled trials (RCTs) with similar experimental and control arms were available, a meta-analysis was conducted using the Review Manager software (RevMan 5.3) provided by the Cochrane Collaboration. For all outcomes, the generic inverse variance model with random effects was used. For time-to-event outcomes, hazard ratios (HR), rather than the number of events at a certain time point, were the preferred statistic for meta-analysis. If the HR and/or its standard error were not reported, they were derived from other information reported in the study, using the methods described by Parmar et al. Statistical heterogeneity was calculated using the  $\chi^2$  test for heterogeneity and the  $I^2$  percentage. A probability level for the  $\chi^2$  statistic less than or equal to 10% ( $p \leq 0.10$ ) and/or an  $I^2$  greater than 50% was considered indicative of statistical heterogeneity.

### Study Design and Quality

The quality of included studies was assessed using the Cochrane Risk of Bias Assessment Tool and other quality features such as the follow-up rate and duration, sample size, and power calculation.

## Methods Used to Formulate the Recommendations

Expert Consensus

## Description of Methods Used to Formulate the Recommendations

### Guideline Developers

Development of this guideline was led by a Working Group of the Head and Neck Disease Site Group (DSG). The DSG members have expertise in surgical oncology, medical oncology, radiation oncology, and health research methodology (see Appendix 1 in the original guideline document for membership). The members of the Working Group were responsible for researching the evidence base, drafting the first version of the recommendations, and leading the response to the external review. All DSG members contributed to the final interpretation of the evidence,

refinement of the recommendations, and approval of the final version of the document.

### Guideline Development Methods

The Program in Evidence-Based Care (PEBC) produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle. This process includes a systematic review, interpretation of the evidence, and draft recommendations by the members of the Working Group, internal review by content and methodology experts, and external review by Ontario clinicians and other stakeholders.

The PEBC uses the Appraisal of Guidelines Research and Evaluation (AGREE) II framework as a methodological strategy for guideline development. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development.

The currency of each document is ensured through periodic review and evaluation of the scientific literature and, where appropriate, the addition of newer literature to the original evidence base. This is described in the PEBC Document Assessment and Review Protocol (see the "Availability of Companion Documents" field). PEBC guideline recommendations are based on clinical evidence, and not on feasibility of implementation; however, a list of implementation considerations such as costs, human resources, and unique requirements for special or disadvantaged populations is provided along with the recommendations for information purposes. PEBC guideline development methods are described in more detail in the PEBC Handbook and the PEBC Methods Handbook (see the "Availability of Companion Documents" field).

### Research Questions

1. In patients with unresected squamous cell carcinoma of the head and neck, what are the chemotherapy regimens that, administered concurrently with conventional or intensified radiotherapy, are superior or equivalent to other regimens on important outcomes such as tumour response rate, survival rate, and organ preservation with fewer toxicity/adverse events?
2. In postoperative patients with squamous cell carcinoma of the head and neck, what is the optimal chemotherapy regimen that can be administered concurrently with conventional radiotherapy?
3. Compared to chemoradiotherapy, can targeted agents or radiosensitizers improve or maintain outcomes, with reduced adverse events/toxicity, when used alone or in addition to primary radiotherapy in the treatment of patients with squamous cell carcinoma of the head and neck?
4. In patients with squamous cell carcinoma of the head and neck, what are the induction chemotherapy regimens that are superior or equivalent to others on important outcomes such as tumour response rate, survival rate, and organ preservation with fewer toxicity/adverse events?
5. What are the subgroups of patients with squamous cell carcinoma of the head and neck that would benefit more than others from postoperative systemic therapy?

## Rating Scheme for the Strength of the Recommendations

Not applicable

## Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

## Method of Guideline Validation

External Peer Review

Internal Peer Review

## Description of Method of Guideline Validation

### Guideline Review and Approval

Internal Review

For the guideline document to be approved, 75% of the content experts who comprise the Head and Neck Cancer Disease Site Group (DSG) membership must cast a vote indicating whether or not they approve the document, or abstain from voting for a specified reason, and of those that vote, 75% must approve the document. In addition, the Program in Evidence-based Care (PEBC) Report Approval Panel (RAP), a three-person panel with methodology expertise, must unanimously approve the document. The DSG and RAP members may specify that approval is conditional, and that changes to the document are required. If substantial changes are subsequently made to the recommendations during external review, then the revised draft must be resubmitted to the RAP and the DSG Panel for approval.

#### External Review

Feedback on the approved draft guideline is obtained from content experts and the target users through two processes. Through the Targeted Peer Review, several individuals with content expertise are identified by the DSG and asked to review and provide feedback on the guideline document. Through Professional Consultation, relevant care providers and other potential users of the guideline are contacted and asked to provide feedback on the guideline recommendations through a brief online survey. This consultation is intended to facilitate the dissemination of the final guidance report to Ontario practitioners.

See Section 5 in the original guideline document for further discussion of the internal and external guideline review process and results.

## Evidence Supporting the Recommendations

### Type of Evidence Supporting the Recommendations

The recommendations are supported by meta-analyses and randomized controlled trials (RCTs).

## Benefits/Harms of Implementing the Guideline Recommendations

### Potential Benefits

Appropriate use of systemic therapy in curative treatment of head and neck squamous cell cancer

See the "Key Evidence" and "Interpretation of Evidence" sections of the original guideline document for a discussion of benefits of specific treatment regimens in particular patient subgroups.

### Potential Harms

- Trials showed that compared to radiotherapy (RT) alone, more toxic effects were reported in the chemoradiotherapy (CRT) groups. The rates of late adverse effects were similar between the trial groups but acute adverse effects appeared to be more common in the chemotherapy groups. In one trial, the incidence of acute adverse effects in the CRT group was doubled compared to RT alone. While hematologic adverse effects were reportedly very mild, mucositis was the most common non hematologic adverse event reported in the trials. Greater number of CRT patients required enteral or parenteral feeding. When the addition of chemotherapy to different fractionations of RT was evaluated, patients in the very accelerated RT group had more acute adverse effects compared with patients who were administered conventional or accelerated RT (84% versus 76% or 69%)  $p=0.0001$ . Postoperatively, the addition of chemotherapy to RT increased the incidence of adverse effects. The tendency of developing a Grade 3 adverse effect was higher in the cisplatin arm (78%) compared to RT alone (46%);  $p=0.001$ .
- Although most of the studies reported a trend towards a higher incidence of adverse events in the intervention groups, the differences in the rates of adverse events and quality of life (QoL) score between the groups were not significant. In one study, the incidence of Grade 3 to 5 infusion reactions and acneiform rash was significantly higher in the cetuximab arm, and these adverse effects seemed to occur mainly in the first five to 15 days of treatment. In another trial, more treatment-related Grade 5 adverse events were reported in the cetuximab arm ( $p=0.05$ ). The higher rates of Grade 3 to 5 skin reactions and mucositis in the cetuximab arm did not remain significant after 90 days post-therapy, but the feeding tube dependency rate at three years was higher in the cetuximab arm (12% versus 7%;  $p=0.05$ ).
- The most common hematologic adverse events (AEs) observed with the use of induction chemotherapy (IC) were myelosuppression, neutropenia, thrombocytopenia, and anemia, while mucositis, fatigue, alopecia, nausea, and dehydration were the common non-hematologic AEs. The rates of hematologic AEs were higher in patients in the IC group. There was a trend for platin/5-fluorouracil regimen to have

significantly more thrombocytopenic AEs in the studies, while the incidence of neutropenia and anemia were greater in docetaxel/cisplatin/5-fluorouracil or other triple regimens.

See the "Key Evidence" and "Interpretation of Evidence" sections of the original guideline document for a discussion of harms of specific treatment regimens in particular patient subgroups.

## Qualifying Statements

### Qualifying Statements

- Care has been taken in the preparation of the information contained in this report. Nevertheless, any person seeking to consult the report or apply its recommendations is expected to use independent medical judgment in the context of individual clinical circumstances or to seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representations or guarantees of any kind whatsoever regarding the report content or its use or application and disclaims any responsibility for its use or application in any way.
- See the original guideline document for qualifying statements related to each recommendation.

#### Important Caveats

- The importance of human papillomavirus (HPV) in the pathogenesis of locally advanced nonmetastatic squamous cell carcinoma of the head and neck (LASCCHN) has been recognized over the past decade. The randomized controlled trials (RCTs) considered in this guideline were conducted without recognition of this important biological prognostic factor. Consequently, the results of individual RCTs should be interpreted cautiously, as inadvertent imbalance in the proportion of patients with HPV-related tumours could influence trial results. The corollary is true: the pooled results of these trials should be applied to patients with HPV-related LASCCHN cautiously, as the optimal treatment approaches for these patients remain to be defined.
- Radiation treatment techniques have technically evolved and become more sophisticated since the RCTs considered in this guideline were conducted. Although it is unlikely that these changes would reduce the efficacy of concurrent drug therapy, they might influence the types and severity of adverse effects.
- The use of drug therapy, especially chemotherapy, in patients with LASCCHN significantly increases the acute and long-term adverse effects of treatment, and these may be life-threatening. Treatment plans incorporating chemotherapy in the curative treatment of patients with LASCCHN should be developed within the context of an appropriate multidisciplinary care team assessment and be supervised by a medical oncologist experienced in treating head and neck cancer.
- Subset analysis of a meta-analysis of individualized patient data reported a diminishing overall survival benefit of concomitant chemotherapy with increasing age such that no benefit was observed beyond age 70 (test for trend,  $p = 0.003$ ). However, diminished event-free survival with age was not observed. Furthermore, in the most recent trials (1994-2000) the proportion of deaths not due to head and neck cancer increased progressively with age from 15% in patients less than 50 to 39% in patients over age 70. In patients with potentially curable LASCCHN over age 70, the decision to add concomitant chemotherapy to curative radiation should be individualized. It may still be a reasonable option to improve overall survival if the probability of death from non-LASCCHN causes is considered low. It may also be a reasonable option if the primary goal of treatment is not overall survival (e.g., organ preservation or to enhance locoregional cancer control). The risks of severe toxicity and interference with the efficient delivery of curative radiation should be considered in every patient.

## Implementation of the Guideline

### Description of Implementation Strategy

#### Implementation Considerations

- Feasibility: In the province of Ontario, access to systemic therapies is well established when the cost of such care is reasonable.
- Equity: One priority of Cancer Care Ontario is to maintain universal (including geographic) access to cancer care. At the moment, the guideline developers do not anticipate that the recommendations would increase inequities in care.
- Provider considerations: Since this guideline is subject to an external review process, it is the guideline developers' assumption that the opinions expressed in this document reflect those of a broad community of clinicians.
- Patient considerations: The recommendations include statements that are focused on patient-centred decisions. A balance between survival

rate, disease control, and long-term adverse effects was considered in making the recommendations.

- System considerations: The recommendations should not increase the burden on the current system of care.

## Implementation Tools

Quick Reference Guides/Physician Guides

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

## Institute of Medicine (IOM) National Healthcare Quality Report Categories

### IOM Care Need

Getting Better

Living with Illness

### IOM Domain

Effectiveness

Patient-centeredness

## Identifying Information and Availability

### Bibliographic Source(s)

Winkvist E, Agbassi C, Meyers B, Yoo J, Chan K, Head and Neck Cancer Disease Site Group. Systemic therapy in the curative treatment of head and neck squamous cell cancer. Toronto (ON): Cancer Care Ontario (CCO); 2016 Aug 10. 51 p. (Program in Evidence-based Care Guideline; no. 5-11). [91 references]

### Adaptation

Not applicable: The guideline was not adapted from another source.

### Date Released

2016 Aug 10

### Guideline Developer(s)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

### Guideline Developer Comment

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario (CCO) and the Ontario

## Source(s) of Funding

The Program in Evidence-based Care (PEBC) is a provincial initiative of Cancer Care Ontario (CCO) supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from the Ontario Ministry of Health and Long-Term Care.

## Guideline Committee

Head and Neck Disease Site Group

## Composition of Group That Authored the Guideline

*Authors:* E. Winkvist, C. Agbassi, B. Meyers, J. Yoo, K. Chan

## Financial Disclosures/Conflicts of Interest

Each disease site group (DSG) member declared professional and financial competing interests in the areas of grants, publications, employment, and other relevant business entities; Appendix 2 in the original guideline document provides further detail. In accordance with the [Program in Evidence-Based Care \(PEBC\) Conflict of Interest Policy](#) , individuals with competing interests were not allowed to participate as members of the Working Group unless otherwise stated.

## Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

## Guideline Availability

Available from the [Cancer Care Ontario \(CCO\) Web site](#) .

## Availability of Companion Documents

The following are available:

- Winkvist E, Agbassi C, Meyers B, Yoo J, Chan K, Head and Neck Cancer Disease Site Group. Systemic therapy in the curative treatment of head and neck squamous cell cancer. Summary. Toronto (ON): Cancer Care Ontario (CCO); 2016 Aug 10. 5 p. (Program in Evidence-based Care Guideline; no. 5-11). Available from the [Cancer Care Ontario \(CCO\) Web site](#) .
- Program in Evidence-based Care handbook. Toronto (ON): Cancer Care Ontario (CCO); 2012. 14 p. Available from the [CCO Web site](#) .
- Program in Evidence-based Care methods handbook. Toronto (ON): Cancer Care Ontario (CCO); 2014 Sep 23. Available from the [Program in Evidence-based Care \(PEBC\) Toolkit Web site](#) .
- Program in Evidence-based Care document assessment and review protocol. Toronto (ON): Cancer Care Ontario (CCO); 2015 Apr 16. 15 p. Available from the [CCO Web site](#) .

## Patient Resources

None available

## NGC Status

This NGC summary was completed by ECRI Institute on January 6, 2017.

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